U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial #:	NDA 21,427 (SN0182, SN0188, SN0189; SDN-1907)
Supplement # (Date):	SUPPL-43 (December 16, 2013); SUPPL-44 (January 31, 2014)
Drug Name:	Cymbalta (duloxetine hydrochloride)
Indication(s):	Generalized Anxiety Disorder (GAD)
Applicant:	Eli Lilly and Company (Lilly)
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Eiji Ishida, M.S.
Concurring Reviewers:	Peiling Yang, Ph.D.; Kooros Mahjoob, Ph. D.
Medical Division:	Division of Psychiatry Products
Clinical Reviewer:	Tiffany Farchione, M.D.
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Keywords: NDA Supplement Review, Pediatric study, Geriatric study, PREA PMR

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1 EXECUTIVE SUMMARY

Two efficacy studies of duloxetine as an acute therapy in special populations, pediatric patients with moderate and severe GAD in Study F1J-MC-HMGI and elderly GAD patients in Study F1J-MC-HMGF, were submitted as part of two supplemental NDAs (new drug applications), NDA 21,427 (SUPPL-43 and SUPPL-44).

In Study HMGI, a flexible dose of Duloxetine 30 to 120 mg QD has been shown to be efficacious as an acute treatment for GAD in a special GAD population consisting of age groups, children (7 – 11 years of age) and adolescents (12 – 17 years of age), in a 10-week double-blind efficacy study, based on the primary efficacy endpoint of the change from baseline to the 10-week endpoint in PARS severity score for GAD.

In Study HMGF, a flexible dose of Duloxetine 30 to 120 mg QD has been shown to be efficacious as an acute treatment for GAD in a special population of elderly GAD patients (65 years old or older), in a 10-week double-blind efficacy study, based both on the primary efficacy endpoint of the change from baseline to the 10-week endpoint in HAMA total score, and the key secondary efficacy endpoint of the change from baseline to the 10-week endpoint in SDS Global Functional Impairment score.

This reviewer recommends that the positive study results of both studies be added in the label.

2 INTRODUCTION

Duloxetine hydrochloride, hereafter referred to as duloxetine, is currently approved in the United States (US) for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), and fibromyalgia, for the management of diabetic peripheral neuropathic pain, and chronic musculoskeletal pain in adults at least 18 years of age.

Eli Lilly and Company (Lilly) submitted a supplemental New Drug Application (NDA) (NDA 21,427: Supplement 43, dated 16 December 2013) to fulfill a Pediatric Research Equity Act [PREA] requirement, the required pediatric study commitment, issued by the Food and Drug Administration (FDA) as part of the 23 February 2007 supplemental NDA approval for the use of duloxetine for the treatment of generalized anxiety disorder (GAD). The sponsor submitted another supplemental NDA (NDA 21,427: Supplement 44, dated 31 January 2014). The Supplement 44 submission included a geriatric study.

Two studies submitted under the current NDA supplements, Studies F1J-MC-HMGI (pediatric) and F1J-MC-HMGF (geriatric), evaluated the safety and efficacy of duloxetine for treatment of GAD in special populations. In the present review, the efficacy of duloxetine as an acute therapy for the geriatric GAD population and for the pediatric GAD population is evaluated based on the two studies.

2.1 Overview

In the pediatric study (Supplement-43), efficacy of duloxetine was evaluated as an acute therapy for generalized anxiety in GAD patients of 7 - 17 years old. On 23 February 2007, Duloxetine was approved for the treatment of GAD in adults at least 18 years of age under supplemental NDA (SUPPL-11). The approval letter included a post-marketing commitment (PMC) for the sponsor to conduct a deferred pediatric study under the Pediatric Research Equity Act (PREA). The requirement was waved for children below the age of 7 years.

In the geriatric study (Supplement-44), efficacy of duloxetine was evaluated as an acute therapy for generalized anxiety in elderly patients with GAD. On 28 July 2008, the Committee for Medicinal Products for Human Use (CHMP) approved for the indication of duloxetine as a treatment for elderly patients with GAD. As part of the approval, the sponsor was requested to conduct this study. In the planning process, the sponsor submitted the protocol of this post-marketing study to the FDA for review.

The key information regarding the two studies, F1J-MC-HMGI (pediatric) and F1J-MC-HMGF (geriatric), is summarized in Table 1.

Table 1: Important elements of Studies included in Efficacy evaluation

Supplement #	**S-43**	**S-44**
Study	**F1J-MC-HMGI**	**F1J-MC-HMGF**
Phase of Development	Phase 3b (PREA PMR study)	Phase 4
Study population	Children (aged 7 through 11 years) and adolescences (aged 12 through 17 years) with GAD	Elderly GAD patients (≥ 65 years old)
Treatment duration	10 weeks (double-blinded phase)	10 weeks (double-blinded phase)
# of Subjects	260 planned 281 randomized 272 ITT patients (as defined by Sponsor) (135 duloxetine, 137 placebo)	288 planned 291 randomized 291 ITT patients (151 duloxetine, 140 placebo)
Treatment	Flexible dosing: 30-120 mg once daily (QD)	Flexible dosing: 30-120 mg once daily (QD)
Country of study sites	Mexico, South Africa, United States	Argentina, Austria, Canada, Germany, Spain, United Kingdom, Mexico, Poland, Puerto Rico, United States
Efficacy endpoints	Primary endpoint: Change from baseline to 10th week in PARS (Pediatric Anxiety Rating Scale) Severity Rating Score for GAD Note: *PARS Severity Rating Score for GAD* is the sum of 5 of the PARS 7 severity/impairment/interference items (2, 3, 5, 6, and 7))	(1) Primary endpoint: Change from baseline to 10th week in HAMA (Hamilton Anxiety Rating Scale) total score (2) Key secondary endpoint: Change from baseline to 10th week in SDS (Sheehan Disability Scale) Global Functional Impairment score

Note: (1) Study F1J-MC-HMGI had Screening phase (Study Period I), Double-blind phase (Study Period II), and Taper phase (Study Period III). (2) Study F1J-MC-HMGI had Screening phase (Study Period I), Double-blind phase (Study Period II), Open-label, Extension phase (Study Period III) and Taper phase (Study Period IV). (3) The sponsor defined "ITT" as patients who had at least one post-baseline value of the pre-specified efficacy endpoint. [Source: CSRs of Studies F1J-MC-HMGI and F1J-MC-HMGF]

Reviewer's Note: As shown in the above table, 281 subjects were randomized in Study F1J-MC-HMGI, although 260 patients were planned to be randomized. Sponsor originally planned to randomize 260 subjects but 21 more subjects were randomized. The discrepancy may appear unusual. (1) Sponsor increased the sample size by 12. Thirteen randomized subjects who had less severe GAD than planned were not supposed to be randomized. Accordingly, Sponsor found the effect size needed to be adjusted to maintain the study power specified in the sample size calculation by increasing the sample size. (2) Sponsor found Site 190 had a serious GCP violation, and replaced the 9 subjects of this site with 9 new subjects. Accordingly, 272 subjects of 281 randomized subjects (12 more subjects than initially planned) were included in the ITT. See Section 3.4.2 for more details.

2.2 Data Sources

The submission SN0182 included CDISC SDTM datasets and ADaM datasets of both studies, which are located in the FDA server:

\\CDSESUB1\evsprod\NDA021427\0182.

After the submission, it was found that the sponsor collected data in their legacy database, and converted them into SDTM datasets. Therefore, the agency requested that the sponsor submit the legacy (raw) data as a filing requirement. The subsequent submissions under SN0188 and SN0189 provided the raw data for Study HMGI and HMGF as required:

The raw (legacy) data of the pediatric study are located in the FDA server:

\\CDSESUB1\evsprod\NDA021427\0188.

The raw (legacy) data of the geriatric study are located in the FDA server:

\\CDSESUB1\evsprod\NDA021427\0189.

Duloxetine was approved for a treatment of GAD patients under NDA 21,427 (Supplement-11). The data of the three efficacy studies of the initial NDA are located at the following FDA server:

\\fdswa150\NONECTD\N21427\S_011\2006-04-27\CRT\Datasets\HMBR,
\\fdswa150\NONECTD\N21427\S_011\2006-04-27\CRT\Datasets\HMDT,
\\fdswa150\NONECTD\N21427\S_011\2006-04-27\CRT\Datasets\HMDU.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

For both studies, this reviewer confirmed the sponsor's efficacy analyses based on the submitted analysis datasets, which were generated from CDISC SDTM datasets. He also verified the sponsor's efficacy results using the legacy data (raw data from the sponsor's clinical database).

Office of Scientific Investigations (OSI) inspected three study sites (Site 340 for Study HMGI, and Sites 907[1] and 600 for Study HMGF). The major issue the inspection identified was that in Study HMGI, three subjects of Site 340 who did not meet the GAD severity inclusion criterion were randomized to duloxetine[2]. This reviewer confirms that the efficacy conclusion of Study HMGI has not been affected by the efficacy results of this site. See Note (2) of Figure 3 for more details.

3.2 Evaluation of Efficacy

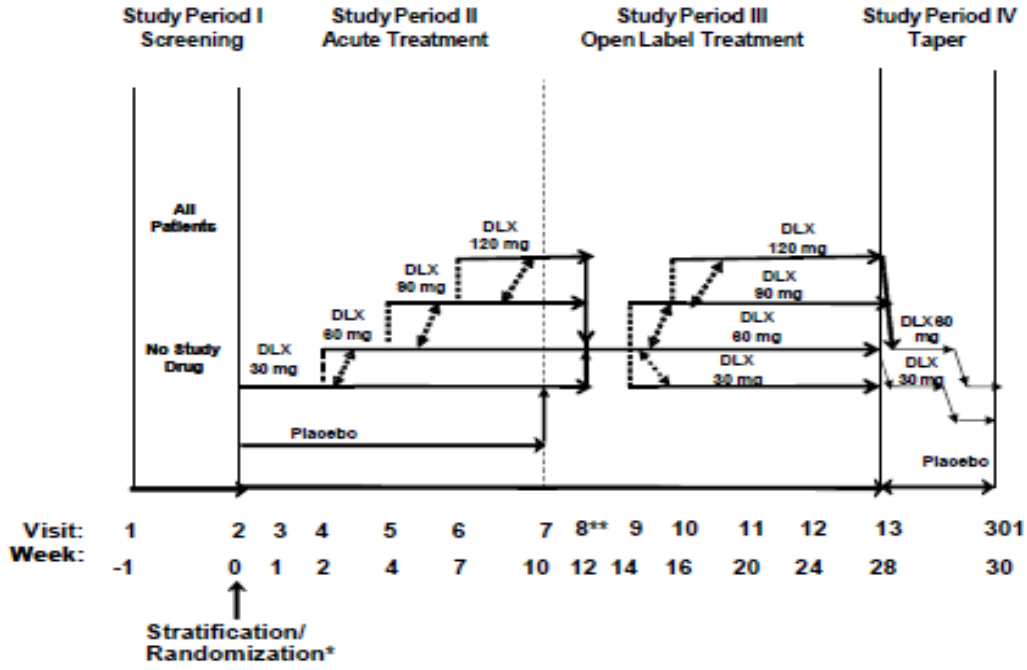
3.2.1 Study Design and Endpoints

Study F1J-MC-HMGI: Study HMGI was a Phase 3b, multicenter, randomized, double-blind, clinical trial of duloxetine versus placebo in children and adolescents meeting DSM-IV-TR, criteria for GAD. This study employed stratified randomization by age group: children (aged 7 through 11 years) and adolescents (aged 12 through 17 years).

The study consisted of 4 periods: a 1-week screening period, a 10-week, double-blind, acute treatment period, an 18-week treatment period consisting of a 16-week open-label and a 2-week tapering period. The total number of randomly assigned patients of this study was anticipated to be approximately 260, with approximately 130 assigned to each of 2 arms: duloxetine (flexible dosing from 30 to 120 mg QD) and placebo. To achieve a balance between the number of randomized children (aged 7 through 11 years) and adolescents (aged 12 through 17 years), enrollment was monitored throughout the study to achieve no less than a 40% complement of children (aged 7 through 11 years). The 10-week, double-blind, acute treatment period (Study Period II) was used to allow a slower dose escalation to the higher duloxetine doses of 90 or 120 mg QD. This slower escalation was intended to improve tolerability. For an illustration of the design, see Figure 1.
The primary efficacy endpoint was the change from baseline to the 10-week endpoint in anxiety symptoms as measured by the PARS Severity Rating Score for GAD. No Key secondary endpoint was planned.

[1] Site 340 and Site 907 were under the same investigator.
[2] This site was reported by OSI (Office of Scientific Investigations) as having had "significant GCP deviations).

Figure 1: Study design of Study HMGI



Abbreviations: DLX=duloxetine

* Patients were stratified by age (children aged 7-11 years or adolescents aged 12-17 years) before randomization into the 2 treatment arms. Enrollment was monitored to achieve no less than 40% total complement of children.

** After Visit 8 and prior to Visit 9, if necessary due to tolerability, a dose decrease may have occurred at an unscheduled visit.

[Source: Figure HMGI.9.1 of the sponsor's CSR (page 31)]

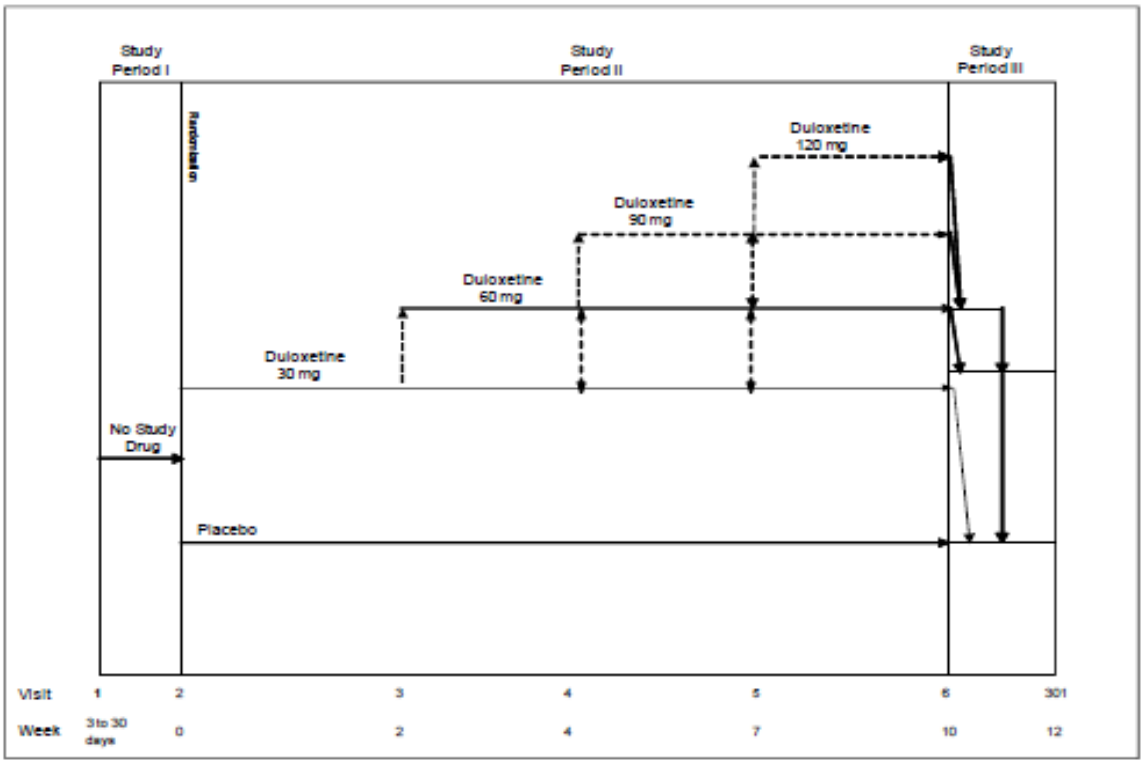
Study F1J-MC-HMGF: Study HMGF was a multicenter, randomized, double-blind, Phase 4 study designed to assess the efficacy of duloxetine 30 to 120 mg QD compared with placebo in the acute treatment of elderly patients (≥65 years old) with GAD. Elderly patients who met criteria for GAD as defined by the DSM-IV TR were eligible to participate in this study.

The study consisted of 3 study periods. Following a 3 to 30 day screening phase (Study Period I), eligible patients were randomly assigned at Visit 2 to groups of flexible dosing of duloxetine (30 to 120 mg QD) and placebo in a 1:1 ratio. A total of 291 patients were randomly assigned to 10 weeks of double-blind treatment (Study Period II). Patients then entered into a 2-week, double-blind, discontinuation-taper phase (Study Period III). To achieve a relative balance across treatment groups with regard to patient age, treatment was randomly assigned by the stratum determined by patients' age (<75 or ≥75 years) at the randomization visit within each study site. For an illustration of the design, see Figure 2.

The primary efficacy endpoint was the change from baseline to the 10-week endpoint in anxiety symptoms as measured by the HAMA total score. The key secondary efficacy endpoint was the

change from baseline to the 10-week endpoint in global functional impairment as measured by Sheehan Disability Scale.

Figure 2: Study design of Study HMGF



Note: Dose increases could only occur at scheduled visits. Dose decreases could occur at both scheduled and unscheduled visits. After a dose was decreased, no further dose increases or decreases could occur. There was a 2-week discontinuation-tapering phase for patients who discontinued treatment at the completion of Visit 6 or who required discontinuation of treatment at or after Visit 4.

[Source: Figure HMGF.9.1 of the sponsor's CSR (page 31)]

3.2.2 Statistical Methodologies

In this section, important statistical aspects of the studies regarding the efficacy analyses are described.

Study F1J-MC-HMGI

1. **Primary objective:** The primary objective of this study was to assess the efficacy of duloxetine compared with placebo in the acute treatment of children and adolescents who met criteria for GAD, based on the mean change from baseline to the 10-week endpoint on the PARS severity score for GAD. The PARS severity score for GAD was derived by summing 5 of the 7 severity/impairment/interference items (2, 3, 5, 6, and 7).
2. **Primary efficacy analysis:** In the primary efficacy analysis, efficacy of duloxetine was compared to efficacy of placebo at the last visit of Study Period II (Visit 7, Week 10). The

comparison was based on a mixed effects repeated measures (MMRM) analysis on the primary endpoint: change from baseline in the PARS severity score for GAD. The MMRM analysis used all the longitudinal observations at each post-baseline visit for the study period of interest. Significance tests were based on least-squares means (LS Means) and Type III sum-of-squares, using a two-sided test with the significance level of 0.05. The model for this analysis included the fixed, categorical effects of treatment, pooled investigator, visit, treatment-by-visit interaction, age category (children aged 7 through 11 years, adolescents aged 12 through 17 years), age category-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction.

3. **Randomization:** The randomization was stratified by age groups, children (aged 7 through 11 years) and adolescents (aged 12 through 17 years).
4. **Multicenter:** All investigative sites with fewer than 2 patients randomized to each treatment (each patient with nonmissing change PARS severity rating score for GAD) were pooled together within each country and considered a single site for analyses. If this resulted in a site still having fewer than 2 patients randomized to each treatment, these sites were pooled together with the next smallest site in that country. If there were no other sites in that country, then these sites would be pooled with the next smallest site in the whole study. Countries were US, Mexico, and South Africa. All analyses used pooled investigative sites.
5. **Missing item:** If a single PARS severity/impairment/interference item was missing, the average of the nonmissing values were substituted for the missing item. If more than 1 item was missing, the total assessment score was set to missing.
6. **Sample size calculation:** Allowing for 10% of patients to have missing post-baseline data, it is assumed that 117 patients per treatment arm will have at least 1 post-baseline assessment. The primary comparison will be between duloxetine (flexible dose) and placebo; therefore, a sample size of 117 in each group will have approximately 80% power to detect an effect size of 0.37 on the PARS severity score for generalized anxiety disorder using a 2 group t-test with a 0.05 two-sided significance level.

   The effect size of 0.37 was determined to be appropriate based on effect sizes on the Hamilton Anxiety Rating Scale for duloxetine in adult GAD studies (Hartford et al. 2007[3]) and historical data for effect sizes on the PARS from studies of other pharmaceutical agents (Geller et al. 2007[4]):
7. **Assessment of the impacts of a sample size increase (12 more patients) and an exclusion of patients from Site 190:** Four versions of analysis sets were listed below (adopted from HMGI.9.8 of the CSR (page 63)).

   Note: In the IND review communication (IND 69,749; SN0116), the FDA requested the sponsor add analyses **c** and **d** described below.

   a. ITT population excluding 13 patients who did not meet inclusion criteria (PARS severity score for GAD <15 at Visits 1 or 2). There were 259 patients in this analysis set (272 minus

[3] Hartford J, Kornstein S, Liebowitz M, Pigott T, Russell J, Detke M, Walker D, Ball S, Dunayevich E, Dinkel J, Erickson J. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active- controlled trial. Int Clin Psychopharmacol. 2007;22(3):167-174.

[4] Geller D, Donnelly C, Lopez F, Rubin R, Newcorn J, Sutton V, Bakken R, Paczkowski M, Kelsey D, Sumner C. Atomoxetine treatment for pediatric patients with attentiondeficit/ hyperactivity disorder with comorbid anxiety disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(9):1119-1127.

13), 256 of which had at least one post-baseline observation. The results of this sensitivity analysis are reported as Sensitivity Analysis 1 in Table HMGI.14.9 of the CSR (page 227).
b. Out of all randomized patients (281), 277 subjects were included in this analysis set, as four patients did not have any post-baseline score. The results of this sensitivity analysis are reported as Sensitivity Analysis 2 in Table HMGI.14.10 of the CSR (page 229).
c. The originally planned randomized patients (the first 260 randomized patients) excluding the 9 patients from the site 190: Out of these 251 patients, 248 with at least one post-baseline score were included in the analysis set. The results of this sensitivity analysis are reported as Sensitivity Analysis 3 in Table HMGI.14.11 of the CSR (page 231).
d. The originally planned randomized patients (the first 260 randomized patients) but replacing the 9 patients from site 190 with the 9 patients who were randomized immediately following the original 260 patients: Out of the 260 patients, 257 were included in the analysis set. The results of this sensitivity analysis are reported as Sensitivity Analysis 4 in Table HMGI.14.12 of the CSR (page 233).

Study F1J-MC-HMGF

1. **Primary objective:** The primary objective was to assess whether duloxetine 30 to 120 mg QD is superior to placebo in the treatment of elderly patients (≥65 years old) with GAD during a 10-week, double-blind, acute therapy phase. The Structured Interview Guide for the Hamilton Anxiety rating scale (SIGH-A) was the required method for collecting the HAMA data in this study.
   Key secondary objective: The key secondary objective was to evaluate the efficacy of duloxetine 30 to 120 mg QD compared with placebo in elderly patients (≥65 years old) during a 10-week, double-blind, acute therapy phase as measured by the mean improvement on the Sheehan Disability Scale (SDS) Global Functional Impairment score.
2. **Primary analysis (for primary efficacy and key secondary efficacy):** The primary efficacy endpoint was defined as the mean change from baseline to 10-week endpoint in anxiety symptoms as measured by the HAMA total score. The key secondary efficacy endpoint was defined as the mean change from baseline to 10-week endpoint in functional impairment improvement as measured by the SDS Global Functional Impairment score. In both analyses, efficacy of duloxetine was compared to efficacy of placebo at the last visit of Study Period II (Visit 6, Week 10). The comparison was based on a mixed effects repeated measures (MMRM) analysis on the respective endpoint. The MMRM analysis used all the longitudinal observations at each post-baseline visit for the study period of interest. Significance tests were based on least-squares means (LS Means) and Type III sum-of-squares, using a two-sided test with the significance level of 0.05. The model for this analysis included the fixed, categorical effects of treatment, pooled investigator, visit, treatment-by-visit interaction, age category (≥75 years old or less), as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction.
3. **Multicenter:** Sites were pooled based on the number of patients having at least 1 baseline and at least 1 post-baseline HAMA total score. All investigative sites with fewer than 2 patients in either treatment group in this category were pooled together within each country

and considered a single site for analyses. If this pooled site still had fewer than 2 patients in either treatment group, then the pooled site was pooled again with the next smallest site in that country. All analyses used pooled investigative sites.

4. **Multiplicity adjustment:** The fixed sequence test was pre-specified and performed under the overall type I error rate control ($\alpha = 0.05$)
5. **Missing item: (1) HAMA total score:** If one or two item of the HAMA total score was missing, then an adjusted total was computed as 14/13*(Observed total score) or 14/12*(Observed total score). If three or more items were missing, then the total score was set to missing. **(2) SDS Global Functional Impairment score:** If the work/school domain was missing because it was not applicable for that patient, then the adjusted score was computed as (3/2)*Sum of scores on social life/leisure and family life/home dpmains. If either of the social life/leisure or family life/home domains was missing, then the Global Functional Impairment score was set missing.
6. **Sample size calculation:** With 144 patients randomized to duloxetine and 144 patients randomized to placebo, this study will have approximately 80% power to detect a 0.35 effect size relative to placebo in the baseline-to-endpoint mean change on the HAMA total score. The assumed effect size was based on HAMA Total Score data collected from patients at least 65 years old in 4 placebo-controlled studies investigating the efficacy of duloxetine compared with placebo in patients with GAD. Effect size in this elderly population was approximately 0.40. The sample size was determined using a 2-sided test with p=.05 and assumed that 10% of the patients will discontinue at Visit 3 without providing post-baseline HAMA data.
7. **Randomization:** The randomization was stratified by age group (≥75 years old or <75 years old).

Study elements common to both studies

Intent-to-Treat (ITT) population: The ITT population was defined as randomized subjects with baseline observation who had at least one post-baseline observation.

Sensitivity Analysis for MAR assumption: The primary analysis method is valid under an ignorable missing data mechanism such as MAR (missing at random), but may not be appropriate if the missing data mechanism is Missing Not At Random (MNAR). For each objective of the primary and key secondary efficacy (Study HMGF), and for the objective of the primary efficacy (Study HMGI), a sensitivity analysis, an analysis with an alternative assumption of the MNAR missing data mechanism, was planned and performed. For this purpose, Sponsor used the selection model of Diggle and Kenward (1994)[5].

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition:

[5] Diggle PD, Kenward MG. Informative dropout in longitudinal data analysis (with discussion) *Appl. Stat*. 1994;43:49–93.

Table 2 and Table 3 provide the patient disposition information taken from the table reported in the respective study CSR. In both studies, the proportion of early terminated patients of the duloxetine group was much the same as that of the placebo group.

Table 2: Patient disposition (Study HMGI)

Study HMGI		Placebo N (%)	Duloxetine N (%)	Total N (%)
	Randomized patients	137 (100.0)	135 (100.0)	272 (100.0)
	Completers	106 (77.4)	104 (77.0)	210 (77.2)
	Early Termination	31 (23.0)	31 (22.6)	62 (22.8)
Reasons for Early Termination				
	Adverse Event	6 (10.7)	7 (9.9)	13 (10.3)
	Patient decision/personal conflict	6 (5.7)	10 (8.6)	16 (7.2)
	Protocol violation	5 (4.3)	5 (2.0)	10 (3.1)
	Lack of efficacy	1 (4.3)	2 (1.3)	3 (2.7)
	Parent/caregiver decision	7 (5.1)	4 (3.0)	11 (4.0)
	Lost to follow-up	6 (4.4)	3 (2.2)	9 (3.3)

Note: Five early terminated patients (one for placebo and four for duloxetine) completed the primary efficacy evaluations at all visits of the acute treatment double-blind period.
[Source: Table HMGI.10.1. (Page 80 of Sponsor's CSR)]

Table 3: Patient disposition (Study HMGF)

Study HMGF		Placebo N (%)	Duloxetine N (%)	Total N (%)
	Randomized patients	140 (100.0)	151 (100.0)	291 (100.0)
	Completers	105 (75.0)	115 (76.2)	220 (75.6)
	Early Termination	35 (25.0)	36 (23.8)	71 (24.4)
Reasons for Early Termination				
	Adverse Event	15 (10.7)	15 (9.9)	30 (10.3)
	Patient decision/personal conflict	8 (5.7)	13 (8.6)	21 (7.2)
	Protocol violation	6 (4.3)	3 (2.0)	9 (3.1)
	Lack of efficacy	6 (4.3)	2 (1.3)	8 (2.7)
	Physician's decision	0	2 (1.3)	2 (0.7)
	Death	0	1 (0.7)	1 (0.3)

Note: Six early terminated patients (two for placebo and four for duloxetine) completed the primary efficacy evaluations at all visits of the acute treatment double-blind period.
[Source: Table HMGF.10.1. (Page 59 of Sponsor's CSR)]

Baseline Demographic Characteristics

Study HMGI: Overall, 46.7% of ITT patients were male and 82.0% of patients were White. The median age of the ITT population was 12.21 years. 47.1% of patients were aged 7 through 11 years and 52.9% were aged 12 through 17 years. Among children (aged 7 through 11 years), 52.3% were male and 47.7% were female. Among adolescents (aged 12 through 17 years), 41.7% were male and 58.3% were female. A total of 49.7% of female patients had reached menarche at baseline.

The demographic and other baseline characteristics are reported in the CSR (Tables HMGI.11.1, pages 88 – 89), and it is stated that here were no statistically significant ($p \leq .05$) differences between treatment groups for any of the baseline patient demographics and patient characteristics.

Study HMGF: Overall, 77.7% of ITT patients were female and 85.6% of patients were White. The median age of the ITT population was 70.39 years. 77.3% of patients were less than 75 years of age.
The demographic and other baseline characteristics are reported in the CSR (Tables HMGF.11.1, pages 67 – 68), and it is stated that statistically significant differences ($p \leq .05$) between treatment groups were observed in the patient demographic variables.

The baseline demographics tables are provided in Appendix of this review.

3.2.4 Results and Conclusions

3.2.4.1 Primary efficacy (Study HMGI)

Table 4 provides efficacy results for the primary analysis, which is based on *PARS severity score for GAD* at each visit for both duloxetine and placebo groups.

For each treatment group and each double-blind visit, the following statistics are listed in the table:

(1) Baseline mean *PARS severity score for GAD* (based on baseline scores of patients who efficacy was assessed at the visit)
(2) Visit-wise mean *PARS severity score for GAD*
(3) Mean difference from baseline (calculated as (2) minus (1))
(4) LS mean of change from baseline score in *PARS severity score for GAD* (which was obtained from the primary analysis)
(5) Difference in LS mean between duloxetine and placebo groups
(6) 95% Confidence Interval for Difference in LS Mean and p value

The means of variables (in (1), (2) and (3)) are based on unadjusted (raw) mean of *PARS severity score for GAD*. The LS means of variables (in (4), (5) and (6)) are least square mean estimates from the primary efficacy analysis (MMRM). The primary efficacy analysis result is based on the p value listed in (6).

The CSR (Table HMGI.11.5, page 100) reports the same results as in Table 4.

The primary analysis conclusion: Duloxetine has shown a statistically significant difference (p value less than 0.001 at 5% significance level), compared to placebo, in the change from baseline (Visit 2) score to the 10-week (Visit 7) endpoint based on *PARS severity score for GAD*.

Table 4: Efficacy of the primary efficacy endpoint at all visits (Study HMGI)

Treatment Group	Visit	# Subjects (dropout rate relative to the previous visit)	Mean of PARS Severity Score for GAD at baseline (Standard deviation)	Mean of PARS Severity Score for GAD (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)	95% Confidence Interval for Difference in LS Mean [*p* value]
Duloxetine	2	135	17.50 (1.98)					
Placebo	2	137	17.37 (2.25)					
Duloxetine	3	135 (0.0%)	17.50 (1.98)	14.71 (3.93)	-2.79 (3.65)	-2.85 (0.31)	-0.22 (0.42)	(-1.05, 0.61) [0.605]
Placebo	3	133 (2.9%)	17.41 (2.24)	14.74 (4.16)	-2.67 (3.67)	-2.63 (0.31)		
Duloxetine	4	130 (3.7%)	17.52 (2.00)	12.48 (4.69)	-5.05 (4.56)	-5.11 (0.35)	-1.22 (0.48)	(-2.18, -0.27) [0.012]
Placebo	4	127 (4.5%)	17.47 (2.25)	13.50 (4.18)	-3.97 (4.07)	-3.89 (0.35)		
Duloxetine	5	122 (6.2%)	17.57 (2.00)	10.43 (4.83)	-7.16 (4.70)	-7.14 (0.41)	-2.30 (0.56)	(-3.40, -1.19) [<.001]
Placebo	5	124 (2.4%)	17.52 (2.23)	12.54 (4.70)	-4.98 (4.78)	-4.84 (0.40)		
Duloxetine	6	117 (4.1%)	17.56 (2.01)	9.10 (5.00)	-8.45 (5.08)	-8.34 (0.46)	-2.07 (0.63)	(-3.32, -0.82) [0.001]
Placebo	6	117 (5.6%)	17.56 (2.24)	11.02 (5.51)	-6.55 (5.39)	-6.27 (0.45)		
Duloxetine	7	107 (8.5%)	17.56 (2.01)	7.45 (5.15)	-10.11 (5.37)	-9.70 (0.50)	**-2.65 (0.70)**	**(-4.03, -1.27) [<.001]**
Placebo	7	108 (7.7%)	17.53 (2.22)	9.96 (5.80)	-7.56 (5.67)	-7.05 (0.50)		

Note: (1) LS Mean (least square mean) was obtained from the pre-specified model (MMRM). (2) Visit 2 was baseline and Visit 7 (Week 10) was the efficacy endpoint. (3) The dropout rates at each visit are calculated relative to the previous visit. (4) The reported confidence intervals and *p* values are unadjusted for multiplicity. (5) In the primary efficacy analysis, the endpoint for the comparison between Duloxetine and Placebo was pre-specified as the change from baseline in HAMA total score to Visit 7 (10 weeks of double-blind phase), and the comparison was based on *Difference in LS Mean* at Visit 7, as calculated by subtracting LS Mean of Placebo from that of Duloxetine. [Source: Reviewer's results]

3.2.4.2 Missing data and their impacts on primary efficacy estimates (Study HMGI)

For each visit, the visit-wise dropout rate was calculated as a dropout rate of each current visit relative to the previous visit (Table 4). The observed data suggests that the dropout rate was not too different between the treatment groups. No outstandingly large leap or difference among the visit-wise dropout rates was observed.

In both treatment groups, the raw mean baseline scores in PARS Severity for GAD were similar throughout the visits.

The ANCOVA Completers analysis is, conventionally, interpreted as a *post hoc* analysis as completers are a study outcome. As shown in the table below, Difference in LS Mean between duloxetine and placebo from the ANCOVA Completers analysis was -2.74, and that from the ANCOVA (LOV) analysis was -2.43. As the difference (-2.74 and -2.43) is small, the observed data may suggest that even though it is believed that not all subjects will meet the MAR assumption, such a possible violation of the assumption had a limited impact on the efficacy analysis result. It is noted that Difference in LS Mean (-2.65) between duloxetine and placebo from the primary analysis (from Table 4) lies between these two values (-2.74 and -2.43).

Table 5: ANCOVA analysis (Completers versus Last Observed Values) (Study HMGI)

Analysis Method	Number of Subjects	Treatment group (Number of Subjects)	LS Mean (Standard Error)	Difference in LS Mean (Standard Error)
ANCOVA (Completers)	215	**Duloxetine** (107)	-10.01 (0.51)	-2.74 (0.69)
		Placebo (108)	-7.27 (0.51)	
ANCOVA (LOV)	268	**Duloxetine** (135)	-8.74 (0.48)	-2.43 (0.66)
		Placebo (133)	-6.32 (0.48)	

Note: The results of ANCOVA LOV (last observed values) analysis are equivalent to those of ANCOVA LOCF (last observation carried forward) analysis, which are reported in the sponsor's CSR (page 103, Table HMGI.11.6). There were 268 subjects who had at least one post-baseline observation.
[Source: Reviewer's results]

Sample size change and GCP violation site (Site 190): The total sample size was increased from 260 to 281 without a pre-specified interim analysis. This was due to two reasons described below.

Sponsor found that, while the study was ongoing, 13 patients who did not meet the baseline symptom severity inclusion criteria on the primary efficacy measure (PARS severity score for GAD) had been randomized. This study was originally planned to randomize 260 patients, but 12 more patients were randomized to account for the potentially reduced effect size from the 13 patients. Accordingly, the sample size was increased from 260 to 272. In addition, significant quality issues were found at one investigative site (Site 190), and as a result, an additional 9 patients were randomized to replace the 9 patients from Site 190. As a consequence, the total number of randomized patients was raised to 281.

Sponsor excluded the 9 patients of Site 190 from all efficacy and safety analyses. Therefore, of the 281 randomized patients, 272 (excluding 9 patients from Site 190) were considered as the ITT population and analyzed for the primary efficacy measure, secondary efficacy measures and safety measures. All patients from Site 190 were included in the patient listings of the CSR.

The FDA objected to Sponsor's proposed sample size increase. In the statistical response to the proposal by the sponsor (IND69,749; SN-0109, SN-124), the following two comments were conveyed to the sponsor via Advice/Information Request email letter, dated 5 December 2012:

- **Sample size change:** We object to your plan to modify the pre-specified sample size. Just because some patients who did not meet one of the inclusion criteria were included in the study, it does not rationalize an increase of the study sample size. A power loss caused by an inclusion of these randomized subjects (about 6% of the planned 260 subjects) may not be substantial. Please let us know the trial status, such as patient enrollment, patient completion.

- **Excluding the nine randomized patients from Site 190:** We have no objection to your plan to replace the 9 randomized patients from Site 190 with new patients from other sites. However, we recommend that you perform analyses both including and excluding patients from Site 190. The Division will also review the primary efficacy analysis that includes Site 190.

However, the study enrollment closed with additional randomized patients before the above comments were received. Thus, the FDA communicated to Sponsor that the appropriateness of the primary efficacy analysis may become a review issue, and suggested that Sponsor include the NDA data submission analyses based on the following analysis sets:
(1) the original 260 patients, but excluding the 9 patients from Site 190; and
(2) the original 260 patients, but with the 9 patients from site 190 replaced by 9 new patients.

This sample size change was not pre-specified. Therefore, the first 260 randomized patients should be considered ITT population. However, it may be necessary to check the impact on the primary efficacy analysis result of a removal of the 9 patients due to the above mentioned GCP violation.

In both cases (1) and (2), the primary analysis conclusion is unchanged. The sample size change did not present a serious issue with the primary analysis result. It is noted that the estimated differences in LS mean of the change from baseline between duloxetine and placebo (-2.51 for (1) and -2.56 for (2)) are much the same. They are close to the estimate of the primary analysis (-2.65). All three standard errors were much the same as well.

(1) The original 260 patients, but excluding the 9 patients from Site 190

Table 6: Primary analysis result without Site 190

Treatment group	Visit	LS Mean (Standard error)	Difference in LS Mean (Standard error)	95% Confidence Interval for Difference in LS Mean [p value]
Duloxetine	3	-2.78 (0.33)	-0.12 (0.44)	(-1.00, 0.75) [0.785]
Placebo	3	-2.66 (0.33)		
Duloxetine	4	-4.96 (0.37)	-1.06 (0.51)	(-2.07, -0.06) [0.039]
Placebo	4	-3.90 (0.37)		
Duloxetine	5	-6.96 (0.43)	-1.95 (0.59)	(-3.11, -0.79) [0.001]
Placebo	5	-5.00 (0.42)		
Duloxetine	6	-8.34 (0.48)	-1.86 (0.67)	(-3.18, -0.55) [0.006]
Placebo	6	-6.48 (0.48)		
Duloxetine	7	-9.57 (0.53)	**-2.51 (0.74)**	**(-3.97, -1.05) [<.001]**
Placebo	7	-7.06 (0.53)		

Note: The same MMRM-based method as in the primary analysis was used.
[Source: Reviewer's results]

(2) The original 260 patients, but with the 9 patients from site 190 replaced by 9 new patients.

Table 7: Efficacy without Site 190 and with an addition of 9 new patients

Treatment group	Visit	LS Mean (Standard error)	Difference in LS Mean (Standard error)	95% Confidence Interval for Difference in LS Mean [p value]
Duloxetine	3	-2.76 (0.31)	-0.15 (0.43)	(-1.00, 0.69) [0.719]
Placebo	3	-2.61 (0.31)		
Duloxetine	4	-4.94 (0.36)	-1.06 (0.50)	(-2.04, -0.09) [0.033]
Placebo	4	-3.88 (0.36)		
Duloxetine	5	-6.94 (0.42)	-2.07 (0.57)	(-3.20, -0.94) [<.001]
Placebo	5	-4.87 (0.41)		
Duloxetine	6	-8.33 (0.47)	-1.99 (0.65)	(-3.28, -0.70) [0.003]
Placebo	6	-6.34 (0.47)		
Duloxetine	7	-9.63 (0.52)	**-2.56 (0.71)**	**(-3.97, -1.15) [<.001]**
Placebo	7	-7.07 (0.51)		

Note: The same MMRM-based method as in the primary analysis was used.
[Source: Reviewer's results]

3.2.4.3 Primary and Key secondary efficacy (Study HMGF)

Primary efficacy: Table 8 provides efficacy results for the primary analysis, which is based on *HAMA total score* at each visit for both duloxetine and placebo groups.

The CSR (Table HMGF.11.9, page 88) reports the same results as in Table 8 below.

Table 8: Efficacy of the primary efficacy endpoint at all visits (Study HMGF)

Treatment Group	Visit	# Subjects (dropout rate relative to the previous visit)	Mean of HAMA Total Score at baseline (Standard deviation)	Mean of HAMA Total Score (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)	95% Confidence Interval for Difference in LS Mean [*p* value]
Duloxetine	2	151	24.62 (6.40)					
Placebo	2	140	24.36 (7.11)					
Duloxetine	3	143 (5.3%)	24.61 (6.21)	19.44 (7.19)	-5.16 (6.39)	-5.45 (0.48)	-1.01 (0.63)	(-2.25, 0.24) [0.112]
Placebo	3	131 (6.4%)	24.41 (7.04)	20.11 (7.18)	-4.31 (5.53)	-4.44 (0.51)		
Duloxetine	4	133 (7.0%)	24.71 (6.23)	14.36 (6.42)	-10.35 (7.44)	-10.44 (0.53)	-2.58 (0.71)	(-3.98, -1.17) [<.001]
Placebo	4	124 (5.3%)	24.57 (7.09)	16.66 (7.05)	-7.92 (7.67)	-7.87 (0.56)		
Duloxetine	5	129 (3.0%)	24.67 (6.33)	11.13 (6.84)	-13.53 (8.56)	-13.58 (0.63)	-3.67 (0.86)	(-5.37, -1.97) [<.001]
Placebo	5	119 (4.0%)	24.87 (7.08)	14.57 (7.63)	-10.29 (9.09)	-9.91 (0.66)		
Duloxetine	6	119 (7.8%)	24.71 (6.34)	8.52 (5.53)	-16.18 (8.36)	-15.86 (0.63)	**-4.17 (0.86)**	**(-5.88, -2.47) [<.001]**
Placebo	6	107 (10.1%)	24.74 (6.95)	12.10 (8.04)	-12.64 (9.81)	-11.69 (0.67)		

Note: (1) LS Mean (least square mean) was obtained from the pre-specified model (MMRM). (2) Visit 2 was baseline and Visit 6 (Week 10) was the efficacy endpoint. (3) The dropout rates at each visit are calculated relative to the previous visit. (4) The reported confidence intervals and *p* values are unadjusted for multiplicity. (5) In the primary efficacy analysis, the endpoint for the comparison between Duloxetine and Placebo was pre-specified as the change from baseline in HAMA total score to Visit 6 (10 weeks of double-blind phase), and the comparison was based on *Difference in LS Mean* at Visit 6, as calculated by subtracting LS Mean of Placebo from that of Duloxetine. [Source: Reviewer's results]

For each treatment group and each double-blind visit, the following statistics are listed in the above table:

(1) Baseline mean *HAMA total score* (based on baseline scores of patients who efficacy was assessed at the visit)
(2) Visit-wise mean *HAMA total score*
(3) Mean difference from baseline (calculated as (2) minus (1))
(4) LS mean of change from baseline score in *HAMA total score* (which was obtained from the primary analysis)

(5) Difference in LS mean between duloxetine and placebo groups
(6) 95% Confidence Interval for Difference in LS Mean and p value

The means of variables (in (1), (2) and (3)) are based on unadjusted (raw) mean of *HAMA total score*. The LS means of variables (in (4), (5) and (6)) are least square mean estimates from the primary efficacy analysis (MMRM). The primary efficacy analysis result is based on the p value listed in (6).

The primary analysis conclusion: Duloxetine has shown a statistically significant difference (p value less than 0.001 at 5% significance level), compared to placebo, in the change from baseline (Visit 2) score to the 10-week (Visit 6) endpoint based on *HAMA total score*.

Sponsor pre-specified a multiplicity adjustment in the hypothesis tests for the primary and key secondary efficacy: The hypothesis test for the key secondary endpoint will be performed only if the hypothesis test for the primary efficacy has been statistically significant. The hypothesis test for the key secondary endpoint was performed.

Key secondary efficacy: Table 9 provides efficacy results for the primary analysis, which is based on *HAMA total score* at each visit for both duloxetine and placebo groups.

The CSR (Table HMGF.11.14, page 105) reports the same results as in Table 9.

For each treatment group and each double-blind visit, the following statistics are listed in the table:

(1) Baseline mean *SDS Global Functional Impairment score* (based on baseline scores of patients who efficacy was assessed at the visit)
(2) Visit-wise mean *SDS Global Functional Impairment score*
(3) Mean difference from baseline (calculated as (2) minus (1))
(4) LS mean of change from baseline score in *SDS Global Functional Impairment score* (which was obtained from the primary analysis)
(5) Difference in LS mean between duloxetine and placebo groups
(6) 95% Confidence Interval for Difference in LS Mean and p value

The means of variables (in (1), (2) and (3)) are based on unadjusted (raw) mean of *SDS Global Functional Impairment score*. The LS means of variables (in (4), (5) and (6)) are least square mean estimates from the key secondary efficacy analysis (MMRM). The key secondary efficacy analysis result is based on the p value listed in (6).

Key secondary analysis conclusion: Duloxetine has shown a statistically significant difference (p value less than 0.001 at 5% significance level), compared to placebo, in the change from baseline (Visit 2) score to the 10-week (Visit 6) endpoint based on *SDS Global Functional Impairment score*.

Table 9: Efficacy of the key secondary efficacy endpoint at all visits (Study HMGF)

Treatment group	# Subjects (dropout rate relative to the previous visit)	Visit	Mean of SDS Global Functional Impairment score at baseline (Standard deviation)	Mean of SDS Global Functional Impairment score (Standard deviation)	Mean Difference from baseline (Standard deviation)	Difference in LS Mean (Standard error)	LS Mean (Standard error)	95% Confidence Interval for Difference in LS Mean [p value]
Duloxetine	151	2	13.72 (7.57)					
Placebo	140	2	14.24 (7.46)					
Duloxetine	140 (7.3%)	3	14.06 (7.53)	11.59 (7.88)	-2.47 (5.79)	-2.37 (0.53)	-0.38 (0.66)	(-1.68, 0.91) [0.560]
Placebo	131 (6.4%)	3	14.18 (7.33)	11.92 (7.36)	-2.26 (6.67)	-2.75 (0.50)		
Duloxetine	133 (5.0%)	4	13.98 (7.51)	8.59 (6.84)	-5.39 (7.30)	-2.98 (0.60)	-2.52 (0.77)	(-4.03, -1.01) [0.001]
Placebo	123 (6.1%)	4	14.18 (7.37)	11.12 (7.47)	-3.06 (7.44)	-5.50 (0.57)		
Duloxetine	128 (3.8%)	5	13.89 (7.50)	6.92 (7.03)	-6.97 (7.29)	-3.58 (0.66)	-3.64 (0.85)	(-5.30, -1.97) [<.001]
Placebo	119 (3.3%)	5	14.43 (7.40)	10.53 (7.49)	-3.91 (8.49)	-7.21 (0.62)		
Duloxetine	119 (7.0%)	6	14.18 (7.41)	5.50 (6.42)	-8.62 (7.45)	-5.37 (0.64)	**-3.23 (0.82)**	**(-4.85, -1.61) [<.001]**
Placebo	107 (10.1%)	6	15.19 (7.15)	8.65 (7.03)	-6.54 (7.35)	-8.60 (0.60)		

Note: (1) LS Mean (least square mean) was obtained from the pre-specified model (MMRM). (2) Visit 2 was baseline and Visit 6 (Week 10) was the efficacy endpoint. (3) The dropout rates at each visit are calculated relative to the previous visit. (4) The reported confidence intervals and *p* values are unadjusted for multiplicity. (5) In the key secondary efficacy analysis, the endpoint for the comparison between Duloxetine and Placebo was pre-specified as the change from baseline SDS Global Functional Impairment score to Visit 6 (10 weeks of double-blind phase), and the comparison was based on *Difference in LS Mean* at Visit 6, as calculated by subtracting LS Mean of Placebo from that of Duloxetine.
[Source: Reviewer's results]

3.2.4.4 Missing data and their impacts on primary efficacy estimates (Study HMGF)

For each visit, the visit-wise dropout rate was calculated as a dropout rate of each current visit relative to the previous visit (Table 8). The observed data suggests that the dropout rate was not too different between the treatment groups. No outstandingly large leap or difference among the visit-wise dropout rates was observed.

In both treatment groups, the raw mean baseline scores in HAMA total scores were similar throughout the visits.

Table 10: ANCOVA analysis (Completers versus Last Observed Values) (Study HMGF)

Analysis Method	Number of Subjects	Treatment group (Number of Subjects)	LS Mean (Standard Error)	Difference in LS Mean (Standard Error)
ANCOVA (Completers)	226	**Duloxetine** (119)	-16.21 (0.65)	-4.15 (0.84)
		Placebo (107)	-12.06 (0.71)	
ANCOVA (LOV)	275	**Duloxetine** (143)	-14.58 (0.70)	-4.18 (0.90)
		Placebo (132)	-10.40 (0.74)	

Note: The results of ANCOVA LOV (last observed values) analysis are equivalent to those of ANCOVA LOCF (last observation carried forward) analysis, which are reported in the sponsor's CSR (page 90, Table HMGF.11.10). There were 275 subjects who had at least one post-baseline observation.
[Source: Reviewer's results]

As shown in Table 10, Difference in LS Mean between duloxetine and placebo from the ANCOVA Completers analysis was -4.15, and that from the ANCOVA (LOV) analysis was -4.18. The observed data may suggest that the dropouts and missing observations had a very limited impact on the efficacy analysis result. It is noted that Difference in LS Mean between duloxetine and placebo from the primary analysis was -4.17.

3.2.4.5 Sensitivity Analysis for MAR assumption

In both studies, to address the impact of missing data mechanisms on the primary efficacy analysis, a sensitivity analysis was performed to compare the results from assuming MAR versus MNAR and check for consistency of treatment contrasts.

Study HMGI: The sponsor reports the pre-specified sensitivity analyses in the CSR (Table HMGI.14.13, page 235). Based on the results from the selection model implemented under MNAR assumption, the statistically significant difference in the mean change from baseline between the duloxetine and placebo treatment groups started at Week 2 ($p \leq .009$), and continued to endpoint (Week 10) during Study Period II ($p < .001$).
From the sponsor's results, there was no evidence suggesting that the probability of missing data depends on the unobserved outcomes, which further supports the MAR assumption of the primary analysis.

Study HMGF: The sponsor reports the pre-specified sensitivity analyses for the primary and key secondary endpoint in the CSR Sensitivity analyses addendum (Tables HMGF.7.2, page 2 and HMGF.7.4, page 11, respectively) as follows: Based on the results from the selection model implemented under the MNAR assumption, a statistically significantly greater mean reduction (improvement) in anxiety symptom severity was observed for patients treated with duloxetine at Visit 6, compared with patients on placebo ($p < .001$).

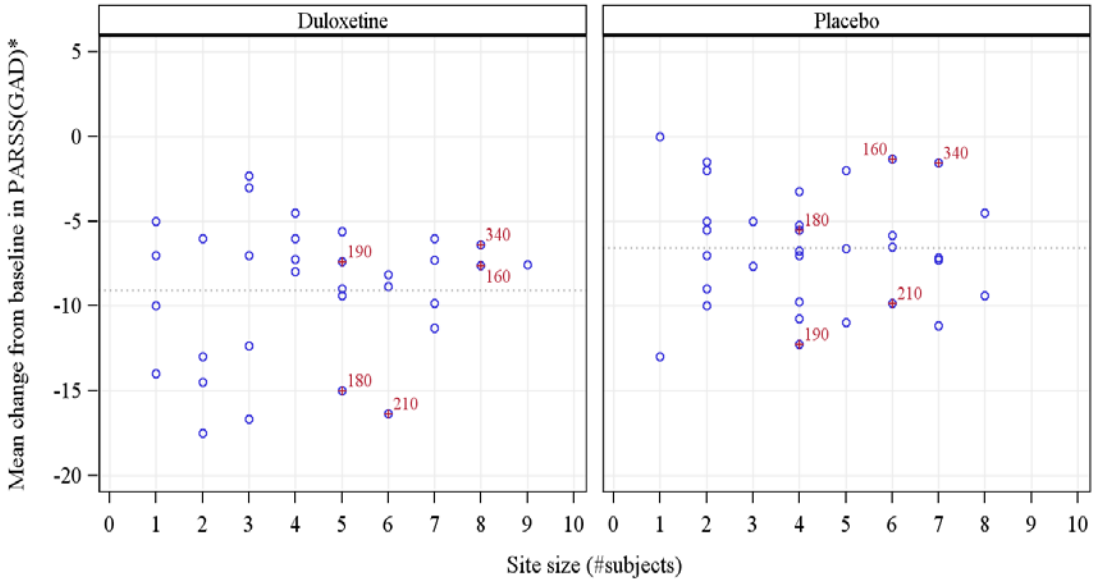
According to the sponsor's results, there was no evidence suggesting that the probability of missing data depends on the unobserved outcomes, which further supports the MAR assumption of the primary analysis.

3.2.4.6 Study site and efficacy

This reviewer created plots of by-site raw mean of the primary efficacy endpoint – change from baseline in PARS severity score for GAD for Study HMGI and HAMA total score for Study HMGF – against the size of site (number of subjects of each site). Last observed values were used to calculate the raw means for each study site.

Study HMGI: As seen in Figure 3, the site identification numbers of four most influential sites favoring duloxetine to placebo (sites 340, 160, 180, and 210) are labelled in the plots. This reviewer conducted the primary analysis for PARS severity score for GAD without each of these sites, and found that none of these sites was influential to such an extent that the primary efficacy conclusion is changed. It is noted from the graph that Site 190 was not favorable to duloxetine in comparison with placebo, thus removing this site from the ITT analysis did favor duloxetine but with or without this site the primary efficacy results are much the same.

Figure 3: Plots of By-site mean change from baseline score in PARS severity score for GAD versus Site sample size (Study HMGI)

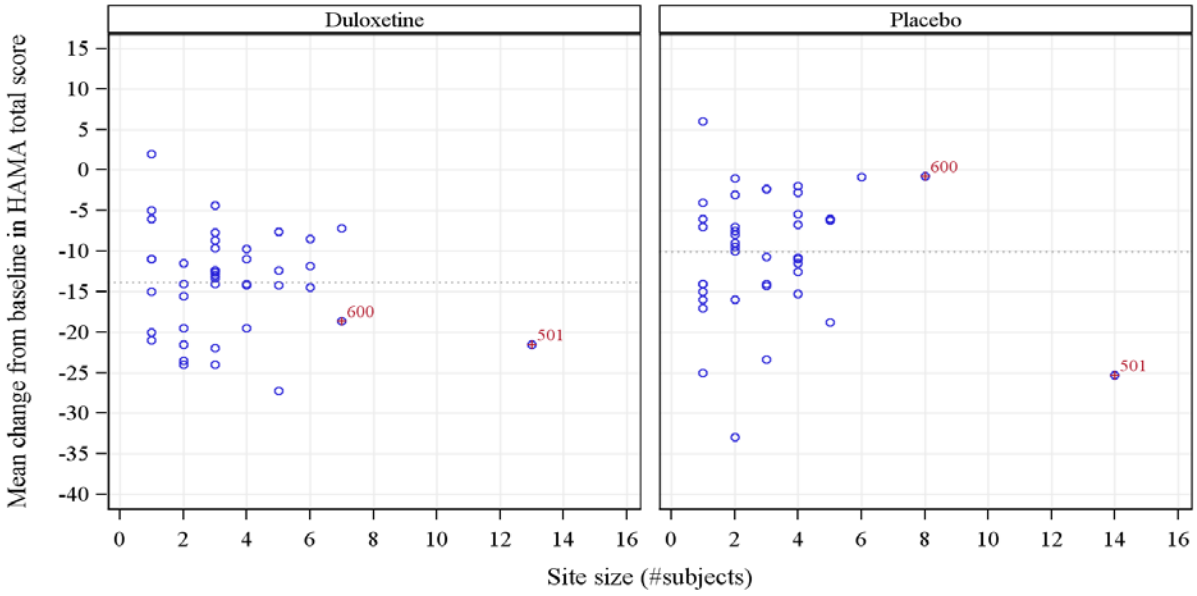


* PARSS(GAD) is PARS Severity score for GAD (Generalized Anxiety Disorder)
Note (1) The dotted line indicates mean of by-site averages of change from baseline in PARSS(GAD). The mean levels were -9.1 (Duloxetine) and -6.4 (Placebo).
Note (2) Sites 340, 180, 160, 210 were most influential in PARS based efficacy assessment. However, the primary efficacy conclusion did not change if any of these sites was excluded.
Note (3) Site 190 was not favorable to duloxetine in the primary efficacy analysis based on PARS Severity score for GAD.

[Source: Reviewer's analysis]

Study HMGF: As seen in Figure 4, the site identification numbers of four most influential sites favoring duloxetine to placebo (sites 600, and 501) are labelled in the plots. This reviewer conducted the primary analysis for HAMA total score without each of these sites, and found that neither of these sites was influential to such an extent that the primary efficacy conclusion is changed.

Figure 4: Plots of By-site mean change from baseline score in HAMA total score versus Site sample size (Study HMGF)



Note (1) The dotted line indicates mean of by-site averages of change from baseline in HAMA total score. The mean levels were -13.9 (Duloxetine) and -10.1 (Placebo).
Note (2) The by-site means of Site 501 duloxetine and placebo groups are visually isolated. These means were close to each other.
Note (3) Site 600 had a placebo-subtracted mean change from baseline most favorable to duloxetine efficacy. However, the primary efficacy conclusion did not change without this site.

[Source: Reviewer's analysis]

3.2.4.7 Efficacy conclusion

Study HMGI: A flexible dose of Duloxetine 30 to 120 mg QD has been shown to be efficacious as an acute treatment for GAD in a special population of children and adolescents with GAD, in a 10-week double-blind efficacy study, based on the primary efficacy endpoint of the change from baseline to the 10-week endpoint in PARS severity score for GAD.

Study HMGF: A flexible dose of Duloxetine 30 to 120 mg QD has been shown to be efficacious as an acute treatment for GAD in a special population of elderly GAD patients, in a 10-week double-blind efficacy study, based on the primary efficacy endpoint of the change from baseline to the 10-week endpoint in HAMA total score, and the key secondary efficacy endpoint of the change from baseline to the 10-week endpoint in SDS Global Functional Impairment score.

4 FINDINGS IN SUBGROUP POPULATIONS

The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory analyses is to assess consistency across subgroups with respect to the primary analysis result. The ANCOVA approach based on last observed observations was used for the subgroup exploratory analyses for gender, country, age group and race. Least square means (LS Means) were used to assess consistency among subgroups. The mean and standard deviation of baseline score of the primary efficacy measure and its change score from baseline to last observed values were also obtained for each subgroup of each treatment group. The subgroup analysis results (LS mean and difference in LS means between duloxetine and placebo) are tabulated in the tables appearing in the following sections. In some cases, the overall ANCOVA LOV results, Difference in LS Mean of -2.43 for Study HMGI (Table 5) and that of -4.18 for Study HMGF (Table 10), are referenced in the descriptions below.

Overall, in each subgroup analysis (gender, race, age group and country), there was no substantially large discrepancy and inconsistency that may be interpreted as suggesting subgroups are prognostic or predictive for the primary efficacy based on PARS severity score for GAD (Study HMGI) and HAMA total score (Study HMGF).

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Subgroup analysis tables (Study HMGI)

Gender: The LS Mean difference from placebo suggests treatment effect in favor of duloxetine in both genders. The difference between male and female (-3.02 versus -1.80) does not seem to be substantial (Table 11).

Table 11: Gender subgroup analysis – ANCOVA LOV (Study HMGI)

Gender	Treatment group	Visit	# Subjects	Mean of PARS Severity Score for GAD at baseline (Standard deviation)	Mean of PARS Severity Score for GAD (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)
Female	Duloxetine	baseline	70	17.31 (1.68)	-	-		
		LOV	70	17.31 (1.68)	8.83 (5.87)	-8.49 (6.18)	-8.75 (0.72)	-1.80 (0.95)
	Placebo	baseline	75	17.11 (2.16)	-	-		
		LOV	73	17.16 (2.13)	10.18 (5.88)	-6.99 (5.82)	-6.95 (0.70)	
Male	Duloxetine	baseline	65	17.71 (2.26)	-	-		
		LOV	65	17.71 (2.26)	8.56 (5.49)	-9.17 (5.47)	-8.86 (0.76)	-3.02 (1.03)
	Placebo	baseline	62	17.69 (2.32)	-	-		
		LOV	60	17.70 (2.35)	11.80 (5.77)	-5.90 (5.86)	-5.84 (0.74)	

Note: LOV indicates "last observed visit".
[Source: Reviewer's results]

Country: From Table 12, the LS Mean difference from placebo of US (-2.47) suggests treatment effect in favor of duloxetine, and was similar in magnitude to the overall LS Mean difference of -2.43 (Table 5). Mexico and South Africa had a small sample size.

Table 12: Country subgroup analysis – ANCOVA LOV (Study HMGI)

Country	Treatment group	Visit	# Subjects	Mean of PARS Severity Score for GAD (Standard deviation)	Mean of PARS Severity Score for GAD (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)
Mexico	Duloxetine	baseline	26	17.42 (1.60)	-	-		
		LOV	26	17.42 (1.60)	9.40 (3.71)	-8.08 (3.68)	-8.55 (0.74)	-2.46 (1.03)
	Placebo	baseline	26	17.15 (1.85)	-	-		
		LOV	25	17.20 (1.87)	11.44 (3.59)	-5.76 (4.19)	-6.08 (0.73)	
United States	Duloxetine	baseline	98	17.52 (2.04)	-	-		
		LOV	98	17.52 (2.04)	8.89 (6.10)	-8.63 (6.29)	-8.57 (0.62)	-2.47 (0.84)
	Placebo	baseline	99	17.43 (2.38)	-	-		
		LOV	96	17.47 (2.37)	11.13 (6.43)	-6.34 (6.36)	-6.10 (0.62)	
South Africa	Duloxetine	baseline	11	17.55 (2.42)	-	-		
		LOV	11	17.55 (2.42)	5.45 (4.63)	-12.09 (4.91)	-11.85 (1.34)	-2.80 (1.81)
	Placebo	baseline	12	17.33 (1.97)	-	-		
		LOV	12	17.33 (1.97)	8.08 (4.19)	-9.25 (3.47)	-9.05 (1.27)	

Note: LOV indicates "last observed visit".
[Source: Reviewer's results]

Table 13: Age group subgroup analysis – ANCOVA LOV (Study HMGI)

Age group	Treatment group	Visit	# Subjects	Mean of PARS Severity Score for GAD (Standard deviation)	Mean of PARS Severity Score for GAD (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)
12-17 years	Duloxetine	baseline	73	17.42 (2.02)	-	-		
		LOV	73	17.42 (2.02)	9.29 (5.70)	-8.15 (5.73)	-8.53 (0.66)	-1.55 (0.89)
	Placebo	baseline	71	17.34 (2.20)	-	-		
		LOV	68	17.43 (2.18)	10.72 (6.16)	-6.71 (6.03)	-6.98 (0.68)	
7-11 years	Duloxetine	baseline	62	17.60 (1.95)	-	-		
		LOV	62	17.60 (1.95)	8.02 (5.61)	-9.58 (5.92)	-9.32 (0.80)	-3.27 (1.02)
	Placebo	baseline	66	17.41 (2.31)	-	-		
		LOV	65	17.38 (2.32)	11.11 (5.58)	-6.28 (5.66)	-6.04 (0.78)	

LOV indicates "last observed visit".
[Source: Reviewer's results]

Age Group: The LS Mean difference from placebo suggests treatment effect in favor of duloxetine in both age groups. The difference between 7-11 years of age and 12-17 years of age does not seem to be substantial (Table 13).

Race: From Table 14, the LS Mean difference from placebo of "White" (-2.26) suggests treatment effect in favor of duloxetine, and was similar in magnitude to the overall LS Mean difference of (-2.65). The subgroups of "American Indian or Alaska Native," "Black or African American," and "Multiple" had a very small sample size.

Table 14: Race subgroup analysis – ANCOVA LOV (Study HMGI)

Race	Treatment group	Visit	# Subjects	Mean of PARS Severity Score for GAD at baseline (Standard deviation)	Mean of PARS Severity Score for GAD (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)
White	Duloxetine	baseline	112	17.48 (1.96)	-	-		
		LOV	112	17.48 (1.96)	8.63 (5.69)	-8.86 (5.87)	-8.86 (0.53)	-2.26 (0.74)
	Placebo	baseline	111	17.40 (2.28)	-	-		
		LOV	107	17.44 (2.27)	10.93 (5.81)	-6.51 (5.71)	-6.59 (0.55)	
Other	Duloxetine	baseline	23	17.61 (2.13)	-	-		
		LOV	23	17.61 (2.13)	9.04 (5.72)	-8.57 (5.85)	-7.84 (1.41)	-2.90 (1.74)
	Placebo	baseline	26	17.27 (2.13)	-	-		
		LOV	26	17.27 (2.13)	10.85 (6.19)	-6.42 (6.44)	-4.93 (1 36)	

Note: (1) LOV indicates "last observed visit". (2) "Other" included American Indian or Alaska Native, Black or African American, and Multiple.
[Source: Reviewer's results]

4.1.2 Subgroup analysis tables (Study HMGF)

Gender: The LS Mean difference from placebo suggests treatment effect in favor of duloxetine in both genders. The difference between male and female (-1.36 versus -4.61) suggests a numerically larger treatment effect in female patients (Table 15).

Table 15: Gender subgroup analysis – ANCOVA LOV (Study HMGF)

Gender	Treatment group	Visit	# Subjects	Mean of HAMA Total Score at baseline (Standard deviation)	Mean of HAMA Total Score (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)
Female	Duloxetine	baseline	114	24.93 (6.23)	-	-		
		LOV	109	24.72 (6.16)	10.17 (7.59)	-14.55 (9.37)	-14.72 (0.87)	-4.61 (1.09)
	Placebo	baseline	112	24.31 (6.78)	-	-		
		LOV	104	24.45 (6.68)	14.53 (9.05)	-9.92 (9.89)	-10.11 (0.87)	
Male	Duloxetine	baseline	37	23.65 (6.89)	-	-		
		LOV	34	24.24 (6.43)	10.35 (5.82)	-13.88 (9.32)	-12.67 (1.28)	-1.36 (1.83)
	Placebo	baseline	28	24.57 (8.43)	-	-		
		LOV	28	24.57 (8.43)	12.04 (7.77)	-12.54 (11.60)	-11.31 (1.74)	

Note: LOV indicates "last observed visit".
[Source: Reviewer's results]

Country: From Table 16, the LS Mean differences from placebo appear to have a large variation among the countries, which may be due to small sample sizes of these countries (Table 16).

Table 16: Country subgroup analysis – ANCOVA LOV (Study HMGF)

Country	Treatment group	Visit	# Subjects	Mean of HAMA Total Score at baseline (Standard deviation)	Mean of HAMA Total Score (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)
Argentina	Duloxetine	2	17	27.06 (5.74)	-	-		
		LOV	15	26.53 (5.91)	12.40 (6.32)	-14.13 (7.18)	-16.36 (1.61)	-1.58 (2.38)
	Placebo	baseline	12	26.67 (4.75)	-	-		
		LOV	12	26.67 (4.75)	14.25 (9.27)	-12.42 (9.82)	-14.79 (1.93)	
Austria	Duloxetine	baseline	13	20.46 (5.29)	-	-		
		LOV	13	20.46 (5.29)	12.85 (6.14)	-7.62 (5.78)	-7.47 (2 22)	-0.13 (2.22)
	Placebo	baseline	10	22.70 (8.67)	-	-		
		LOV	9	21.56 (8.35)	13.33 (5.89)	-8.22 (5 61)	-7.34 (2 37)	

Country	Treatment group	Visit	# Subjects	Mean of HAMA Total Score at baseline (Standard deviation)	Mean of HAMA Total Score (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)
Canada	Duloxetine	baseline	10	23.80 (4.49)	-	-		
		LOV	10	23.80 (4.49)	10.80 (7.48)	-13.00 (9.25)	-13.10 (3.38)	-2.55 (4.33)
	Placebo	baseline	8	23.13 (7.51)	-	-		
		LOV	8	23.13 (7.51)	13.75 (9.62)	-9.38 (7 25)	-10.55 (4.17)	
Germany	Duloxetine	baseline	20	22.80 (4.40)	-	-		
		LOV	19	23.11 (4.29)	11.47 (7.65)	-11.63 (7.59)	-10.97 (1.70)	-4.71 (2.32)
	Placebo	baseline	20	19.20 (5.20)	-	-		
		LOV	19	19.47 (5.19)	14.53 (7.76)	-4.95 (8 20)	-6.26 (1.74)	
Spain	Duloxetine	baseline	9	27.11 (3.76)	-	-		
		LOV	9	27.11 (3.76)	15.00 (12.65)	-12.11 (11.88)	-14.15 (4.14)	-2.96 (5.77)
	Placebo	baseline	9	26.33 (3.94)	-	-		
		LOV	9	26.33 (3.94)	14.67 (13.21)	-11.67 (11.75)	-11.19 (4.14)	
United Kingdom	Duloxetine	baseline	10	20.20 (4.16)	-	-		
		LOV	10	20.20 (4.16)	9.80 (4.78)	-10.40 (6.17)	-10.52 (2.19)	-8.53 (3.48)
	Placebo	baseline	7	22.29 (5.53)	-	-		
		LOV	7	22.29 (5.53)	19.76 (8.77)	-2.52 (7.79)	-1.99 (2 61)	
Mexico	Duloxetine	baseline	21	25.86 (9.70)	-	-		
		LOV	18	26.11 (8.91)	7.78 (7.45)	-18.33 (11.67)	-18.29 (2.31)	0.52 (2.35)
	Placebo	baseline	21	28.33 (10.21)	-	-		
		LOV	19	29.37 (9.69)	7.74 (6.33)	-21.63 (10.14)	-18.80 (2.44)	
Poland	Duloxetine	baseline	27	25.63 (3.86)	-	-		
		LOV	25	25.84 (3.94)	8.48 (5.33)	-17.36 (7.23)	-18.06 (1.52)	-8.59 (1.96)
	Placebo	baseline	29	24.93 (4.22)	-	-		
		LOV	25	25.08 (4.14)	16.88 (8.02)	-8.20 (8.08)	-9.47 (1.52)	
Puerto Rico	Duloxetine	baseline	7	32.00 (5.42)	-	-		
		LOV	7	32.00 (5.42)	6.43 (7.46)	-25.57 (10.78)	-25.85 (3.54)	-1.83 (4.50)
	Placebo	baseline	5	29.40 (8.79)	-	-		
		LOV	5	29.40 (8.79)	7.80 (5.36)	-21.60 (11.10)	-24.02 (3.69)	
United States	Duloxetine	baseline	17	23.06 (7.42)	-	-		
		LOV	17	23.06 (7.42)	8.94 (6.18)	-14.12 (9.23)	-13.01 (2.08)	-7.26 (2.54)
	Placebo	baseline	19	23.00 (6.62)	-	-		
		LOV	19	23.00 (6.62)	15.42 (9.38)	-7.58 (8.05)	-5.75 (2 30)	

Note: LOV indicates "last observed visit".
[Source: Reviewer's results]

Age Group: The LS Mean difference from placebo suggests treatment effect in favor of duloxetine in both age groups, but in the subgroup of "≥75 years of age," the difference between duloxetine and placebo in LS mean was much greater (Table 17). It appears that this was due to the low baseline mean of the placebo patients of ≥75 years of age.

Table 17: Age group subgroup analysis – ANCOVA LOV (Study HMGF)

Age group	Treatment group	Visit	# Subjects	Mean of HAMA Total Score at baseline (Standard deviation)	Mean of HAMA Total Score (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)
<75 years	Duloxetine	baseline	114	24.75 (6.40)	-	-		
		LOV	108	24.80 (6.13)	10.43 (7.64)	-14.37 (9.74)	-13.86 (0.80)	-3.60 (1.09)
	Placebo	baseline	111	25.13 (7.12)	-	-		
		LOV	104	25.22 (7.08)	13.80 (9.17)	-11.42 (10.48)	-10.26 (0.83)	
>=75 years	Duloxetine	baseline	37	24.22 (6.45)	-	-		
		LOV	35	24.03 (6.50)	9.57 (5.63)	-14.46 (8.07)	-14.57 (0.99)	-6.53 (1.52)
	Placebo	baseline	29	21.45 (6.36)	-	-		
		LOV	28	21.71 (6.31)	14.76 (7.52)	-6.96 (8.82)	-8.04 (1.20)	

Note: LOV indicates "last observed visit".
[Source: Reviewer's results]

Race: From Table 18, the LS Mean difference from placebo of "White" (-4.53) suggests treatment effect in favor of duloxetine, and was similar in magnitude to the overall LS Mean difference of -4.18 (Table 10). The subgroup of "American Indian or Alaska Native," had a very small sample size.

Table 18: Race subgroup analysis – ANCOVA LOV (Study HMGF)

Race	Treatment group	Visit	# Subjects	Mean of HAMA Total Score at baseline (Standard deviation)	Mean of HAMA Total Score (Standard deviation)	Mean Difference from baseline (Standard deviation)	LS Mean (Standard error)	Difference in LS Mean (Standard error)
White	Duloxetine	baseline	129	24.05 (5.95)	-	-		
		LOV	123	24.15 (5.79)	10.87 (7.09)	-13.28 (8.78)	-14.00 (0.74)	-4.53 (0.97)
	Placebo	baseline	120	23.52 (6.17)	-	-		
		LOV	114	23.50 (6.14)	14.77 (8.63)	-8.73 (9.00)	-9.46 (0.78)	
American Indian or Alaska Native	Duloxetine	baseline	17	28.35 (8.43)	-	-		
		LOV	15	27.73 (8.51)	6.93 (7.48)	-20.80 (11.23)	-20.31 (3.16)	-0.09 (2.66)
	Placebo	baseline	18	29.56 (10.54)	-	-		
		LOV	16	30.94 (9.77)	7.38 (6.62)	-23.56 (9.77)	-20.22 (3.22)	

Note: (1) LOV indicates "last observed visit". (2) The sample size of Black or African American was very small. The result of this subgroup was not included in the table. [Source: Reviewer's results]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In both studies, two age subgroups were used as a randomization factor for stratified randomization. In both trials, each age subgroup suggested treatment effect in favor of drug, but with different observed magnitudes across the age groups. The exploratory subgroup analyses (Section 4 of this review) may suggest a hypothetical difference in efficacy between the two age groups (7 – 11 years of age and 12 – 17 years of age for Study HMGI and 65 – 74 years of age and 75 years old or older for Study HMGF), but this should not be considered generalizable to the patient population.

5.2 Conclusions and Recommendations

In Study HMGI, a flexible dose of Duloxetine 30 to 120 mg QD has been shown to be efficacious as an acute treatment for GAD in a special GAD population consisting of age groups, children (7 – 11 years of age) and adolescents (12 – 17 years of age), in a 10-week double-blind efficacy study, based on the primary efficacy endpoint of the change from baseline to the 10-week endpoint in PARS severity score for GAD.

In Study HMGF, a flexible dose of Duloxetine 30 to 120 mg QD has been shown to be efficacious as an acute treatment for GAD in a special population of elderly GAD patients (65 years old or older), in a 10-week double-blind efficacy study, based both on the primary efficacy endpoint of the change from baseline to the 10-week endpoint in HAMA total score, and on the key secondary efficacy endpoint of the change from baseline to the 10-week endpoint in SDS Global Functional Impairment score.

This reviewer recommends that the positive study results of both studies be added in the label.

APPENDICES

Baseline Demographic Characteristics

Study HMGI

Demographic variable	Statistics	Placebo	Duloxetine	Total
Age	Number of Subjects	135	137	272
	Mean	12.55	12.20	12.37
	Sd	2.96	2.90	2.93
	Minimum	7.00	7.10	7.00
	Median	12.21	12.21	12.21
	Maximum	17.59	17.78	17.78
Height	Number of Subjects	135	137	272
	Mean	151.79	151.88	151.83
	Sd	16.13	16.00	16.03
	Minimum	102.00	116.50	102.00
	Median	153.50	152.40	153.00
	Maximum	189.00	188.00	189.00
Weight	Number of Subjects	135	137	272
	Mean	52.83	53.59	53.21
	Sd	23.84	23.28	23.52
	Minimum	22.70	21.20	21.20
	Median	47.80	52.20	50.20
	Maximum	165.10	126.00	165.10

Note: Sd denotes standard deviation.
[Source: Reviewer's results]

Demographic variable	Subgroup	Placebo	Duloxetine	Total
Gender	Female	70 (51.85)	75 (54.74)	145 (53.31)
	Male	65 (48.15)	62 (45.26)	127 (46.69)
	Total	135	137	272
Age group	12-17 years	73 (54.07)	71 (51.82)	144 (52.94)
	7-11 years	62 (45.93)	66 (48.18)	128 (47.06)
	Total	135	137	272
Race	American Indian or Alaska Native	7 (5.19)	6 (4.38)	13 (4.78)
	Asian	1 (0.74)	1 (0.73)	2 (0.74)
	Black or African American	9 (6.67)	10 (7.30)	19 (6.99)
	Multiple	6 (4.44)	9 (6.57)	15 (5.51)
	White	112 (82.96)	111 (81.02)	223 (81.99)
	Total	135	137	272
Ethnicity	Hispanic or Latino	37 (27.41)	40 (29.20)	77 (28.31)
	Not Applicable	10 (7.41)	9 (6.57)	19 (6.99)
	Not Hispanic or Latino	88 (65.19)	88 (64.23)	176 (64.71)
	Total	135	137	272
Country	Mexico	26 (19.26)	26 (18.98)	52 (19.12)
	United States	98 (72.59)	99 (72.26)	197 (72.43)
	South Africa	11 (8.15)	12 (8.76)	23 (8.46)
	Total	135	137	272

Note: The figure in ( ) indicates the proportion (percentage) of patients of each subgroup in the total number of patients of the respective treatment group.
[Source: reviewer's results]

Study HMGF

Demographic variable	Statistics	Placebo	Duloxetine	Total
Age	Number of Subjects	140	151	291
	Mean	71.70	71.43	71.56
	Sd	5.04	5.39	5.22
	Minimum	64.93	64.92	64.92
	Median	70.58	69.92	70.39
	Maximum	90.61	86.09	90.61
Height	Number of Subjects	140	150	290
	Mean	160.79	161.64	161.23
	Sd	8.29	9.02	8.67
	Minimum	139.00	140.00	139.00
	Median	160.50	162.00	161.00
	Maximum	182.00	187.00	187.00
Weight	Number of Subjects	140	151	291
	Mean	72.06	74.29	73.22
	Sd	14.48	15.11	14.83
	Minimum	43.00	40.00	40.00
	Median	71.50	74.00	73.00
	Maximum	110.00	131.00	131.00

Note: Sd denotes standard deviation.
[Source: Reviewer's results]

Demographic variable	Subgroup	Placebo (%)	Duloxetine (%)	Total (%)
Gender	Female	112 (80.00)	114 (75.50)	226 (77.66)
	Male	28 (20.00)	37 (24.50)	65 (22.34)
	Total	140	151	291
Age group	<75 years	111 (79.29)	114 (75.50)	225 (77.32)
	>=75 years	29 (20.71)	37 (24.50)	66 (22.68)
	Total	140	151	291
Race	Missing	2 (1.43)	0 (0.00)	2 (0.69)
	American Indian or Alaska Native	18 (12.86)	17 (11.26)	35 (12.03)
	Black or African American	0 (0.00)	5 (3.31)	5 (1.72)
	White	120 (85.71)	129 (85.43)	249 (85.57)
	Total	140	151	291
Ethnicity	Hispanic or Latino	47 (33.57)	55 (36.42)	102 (35.05)
	Not Hispanic or Latino	93 (66.43)	96 (63.58)	189 (64.95)
	Total	140	151	291
Country	Argentina	12 (8.57)	17 (11.26)	29 (9.97)
	Austria	10 (7.14)	13 (8.61)	23 (7.90)
	Canada	8 (5.71)	10 (6.62)	18 (6.19)
	Germany	20 (14.29)	20 (13.25)	40 (13.75)
	Spain	9 (6.43)	9 (5.96)	18 (6.19)
	United Kingdom	7 (5.00)	10 (6.62)	17 (5.84)
	Mexico	21 (15.00)	21 (13.91)	42 (14.43)
	Poland	29 (20.71)	27 (17.88)	56 (19.24)
	Puerto Rico	5 (3.57)	7 (4.64)	12 (4.12)
	United States	19 (13.57)	17 (11.26)	36 (12.37)
	Total	140	151	291

Note: The figure in ( ) indicates the proportion (percentage) of patients of each subgroup in the total number of patients of the respective treatment group.
[Source: reviewer's results]

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/s/

EIJI ISHIDA
09/05/2014

PEILING YANG
09/08/2014

KOOROS MAHJOOB
09/08/2014
I concur with the review.